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EXAMINER	
AUDET, MAURY A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,914	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 34-35 are rejected below based on art.

However, as to claims 1-33 and 36, the claimed invention is drawn to compositions comprising 1.5 molar amount or more of an ANY acid [or ANY base] than the active agent (further comprising ANY polymer which is also an acid, see claim 15 to lactic acid or glycolic acid). Hyun et al. (US 5100669) and Hutchinson (US 5889110) teach all the compound elements presently claimed, the known LHRH derivative of SEQ ID NO: 1, in claim 8, and the 1.5 molar amount or more ratio and the other routinely modifiable variables of the these known compounds (ranges/amounts). WO 93/24150 (CORIXA CORP.) is merely cited of record as teaching the claimed LHRH antagonist of SEQ ID NO: 1 in claim 8.

However, Hutchinson notes that a stronger acid polymer, as presently contemplated in claim 15, can completely cancel-out the effect of a weaker acid, as it appears Applicant has used in testing (polymer of D,L Lactic Acid v. acid of Glacial Acetic Acid)? Thus, the invention is not deemed to have been enabled/distinctly claimed in light of the specification, and it questioned especially as to it's enablement of producing a "stabilized" (claim 2) "sustained release composition" (claim 1) as presently claimed, deemed to be the objective of the invention, since all components (but for molar amount of acid/base: active agent) are otherwise well known genuses (active agents, acids/bases, polymers), as provided in Hutchinson, routinely used together, which would otherwise be obvious, if the molar amount were deemed a routinely optimizable limitation, as it is generally viewed as by those of ordinary skill in the art; absence evidence to the contrary of some unexpected results with specific compounds/amounts thereof; which is not clear on the record as being found here.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyon et al. (US 5100669) in view of Hutchinson (US 5889110), or vice versa.

Both Hyon et al. and Hutchinson teach a method of making a sustained release composition of active agent/acid or base/polymer, BUT FOR (though arguably inherently present) not expressly teaching that the acid or base is in an amount of 0.1 to about 20% by weight of solution. Hyon et al. does not expressly teaching well known salt forms of active agents (which Hutchinson herein addresses).

Hyon et al. (entire document; especially Example 6 and Summary of the Invention bottom of column 2):

EXAMPLE 6

A solution of L-lactic acid-glycolic acid copolymer (copolymerization ratio; 80:20) having a weight average molecular weight of 12,000 (2 g) dissolved in glacial acetic acid (20 ml) and a solution of luteinizing hormone releasing hormone (LHRH; N-Ac[D-P-Cl-Phe.sup.1,2, D-Trp.sup.3, D-Arg.sup.6, D-Ala.sup.10 |LH-RH) (200 mg) dissolved in distilled water (2 ml) were mixed with each other while stirring with magnetic stirrer. The mixture did not become cloudy and remained still clear, showing a complete dissolution of both the polymer and the active substance. This solution was added dropwise to sesame oil (200 ml) containing 1 wt % of lecithin as a surfactant while stirring with a propeller type stirrer and further emulsified with a ultrasonic homogenizer. After acetic acid and water were evaporated with heating at 40.degree. to 60.degree. C., the residue was centrifuged, washed with n-hexane and dried to prepare polylactic acid type microspheres containing LHRH with an average particle size of from 0.5 to 5 .mu.m.

Under such circumstances, the present inventors have intensively studied to develop an improved process for preparing of a release-controlled polylactic acid type preparation which is simple and can afford a stable release of an active substance, and have found that there can be obtained a microspherical preparation which can attain a sustained release of an active substance for a long period of time with avoiding the undesirable occurrence of bursting. The process is directed to preparing a solution of a water soluble physiologically active substance and polylactic acid uniformly dissolved in a mixed solvent comprising a hydrophilic organic solvent and water or in an organic acid, mixing the solution with a poor solvent which is immiscible with said mixed solvent or organic acid to give an emulsion, and then subjecting the mixture to solvent evaporation drying.

An object of the present invention is to provide polylactic acid type microspheres containing a water soluble physiologically active substance, having a high rate of incorporation of employed active substance into said microspheres, and having a mean particle size of from about 0.01 .mu.m to about, 300 .mu.m, showing, in vitro elution test in phosphate buffer of pH 7.4 at 37.degree. C., not more than 30% of an eluted amount of said physiologically active substance based on the content of said physiologically active substance in the polylactic acid type microspheres after 24 hours, and thus enabling a stable sustained release of the active substance over a long period of time.

Hutchinson teach salts of LHRH as active agent (entire document; especially claim 4, 45):

4. A composition as claimed in claim 2 wherein the basic peptide drug is a synthetic analogue of luteinising hormone releasing hormone, selected from the group consisting of buserelin ([D-Ser(Bu.sup.t).sup.6, des-Gly-NH.sub.2.sup.10]-LHRH(1-9)NHEt), deslorelin ([D-Trp.sup.6, des-Gly-NH.sub.2.sup.10]-LHRH(1-9)NHEt), fertirelin ([des-Gly-NH.sub.2.sup.10]-LHRH(1-9)NHEt), goserelin ([D-Ser(Bu.sup.t).sup.6, Azgly.sup.10]-LHRH), histrelin ([D-His(Bzl).sup.6, des-Gly-NH.sub.2.sup.10]-LHRH(1-9)NHEt), leuprorelin ([D-Leu.sup.6, des-Gly-NH.sub.2.sup.10]-LHRH(1-9)NHEt), lutrelin ([D-Trp.sup.6, MeLeu.sup.7, des-Gly-NH.sub.2.sup.10]-LHRH(1-9)NHEt), nafarelin ([D-Nal.sup.6]-LHRH), and tryptorelin ([D-Trp.sup.6]-LHRH), and **pharmacologically active salts thereof.**

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use an amount of 0.1 to about 20% solution of and acid (e.g. glacial acetic acid) in a sustained release composition with an active agent (e.g. LHRH, leuprolide), or salt thereof, and polymer (e.g. D,L lactic acid) in Hyon et al. based the advantageous teachings to the same and if not inherently simply by amount noted above, the routinely optimizable amount of 0.1 to about 20% solution absent evidence to the contrary of some unexpected result thereof, as well as salts of the active agent based on Hutchinson's teachings to the same, in a composition directed to the same compounds therein.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112 1st Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-33 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as not being enabled for:

1. A (stabilized) "sustained release composition", as presently claimed and based on the claimed 1.5 molar amount of acid/base to active agent (peptide luprolide) as read based on test data in description WITHOUT clear evidence what polymer is to be used so not to cancel out the effect of the acid/base on the active agent (e.g. peptide), IF IT WERE a stronger acid than the acid/base for stabilizing the active agent (e.g. peptides), based on the Hutchinson et al. reference (US 5889110). Thus, the invention as claimed is not enabled until the polymer to acid/base issue is addressed or amendment with support made hereto qualify the same, in order that the breadth of the invention as claimed is in fact enabled, such that the skilled artisan can be certain the polymer to be used with the acid/base at 1.5 molar amount would exert the "stabilization" of the claimed 'sustained release composition".

II. Or under a scope of enablement issue, as to the active agents that can be stabilized based on the 1.5 molar amount or more of acid/base thereto. Only peptide as active agents, e.g. LHRH derivatives (claim 7), specifically leuprolide peptide (claim 8) are shown to be tested. Although the results shown can be deemed to extend to other peptides, there is no evidence these results the 1.5 molar amount or more of acid/base would 'stabilize' a non-peptide active agent.

III. Also under a scope of enablement issue, as to WHAT "an acid or base" is capable of being used "in a molar amount of 1.5 or more times" v. WHAT polymer, and the latters effect on the former if a stronger acid, as is entirely possible as claimed. HERE THE TEST RESULTS ALL SEEM TO BE RUN WITH THE ONLY AN ACID [NO BASE] OF GLACIAL ACETIC ACID AND ONLY A POLYMER OF D,L-LACTIC ACID. It is uncertain without undue experimentation if ANY acid (or base) or ANY polymer would carry out the same, but for those tested. [As opposed to the peptides used, even though only leuprolide acetate was used]. Applicant is asked to address with evidence how it could be certain without undue experimentation that ANY acid (or ANY base, not tested) and ANY polymer would work, especially without the latter cancelling out the former. OR amend the claims to be drawn to the specific acid and polymer tested.

Until such is addressed the invention as claimed does not reasonably provide enablement for the invention as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to 1.5 molar amount ratio of acid/base:active agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims.
2. The nature of the invention
3. The state of the prior art;
4. The level of one of ordinary skill

5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure;
See: In re Wands USPQ2d 1400 (CAFC 1988): (1-2)

The relevant factors necessary to establish the undue experimentation deemed necessary to practice the present invention as claimed are developed below.

The breadth of the claims and the nature of the invention: discussed in full above.

Namely, the claimed invention is drawn to compositions comprising 1.5 molar amount or more of an acid or base than the active agent (further comprising a polymer which is also an acid, see claim 15 to lactic acid or glycolic acid). Hutchinson et al. (US 5889110) teach all the elements but for the 1.5 molar amount or more ratio. However, upon a review of the present description, the tests run and amounts therein, do not evidence that Applicant did either? In fact, Hutchinson notes that a stronger acid polymer, as presently contemplated in claim 15, can completely cancel-out the effect of a weaker acid, as it appears Applicant has used in testing? Thus, the invention is not deemed to have been distinctly claimed in the light of the specification, and it questioned as to it's enablement of producing a "stabilized" (claim 2) "sustained release composition" (claim 1) as presently claimed, deemed to be the objective of the invention, since all components (but for molar amount of acid/base: active agent) are otherwise well known genuses (active agents, acids/bases, polymers) routinely used together, which would other be obvious, if the molar amount were deemed a routinely optimizable limitation, as it is generally viewed as by those of ordinary skill in the art; absence evidence to the contrary of some unexpected results with specific compounds/amounts thereof; which is not clear on the record as being found here.

The state of the prior art and the level of predictability in the art:

Hutchinson (US 5889110) teach (entire document as to teaching all compounds presently claimed in composition but for 1.5 or more molar amount of acid(base):active agent (peptide); especially col.'s 3-4) **that stronger acids (e.g. polymer here) can cancel out effect of weaker acids used to stabilize an active agent (such as a peptide of luprolide into it's acetate form):**

> Similar difficulties exist with attempts to form salts of peptides and polyesters using organic solvents, unless the peptide has some solubility or swellability in the solvent. The solubility properties of polyesters and peptides are totally different. Solvents which dissolve the peptide, such as water, are complete non-solvents for the polyester; and, in general, good solvents for the polyester, such as dichloromethane, are complete non-solvents for the peptide. Those solvents which can dissolve both the peptide and the polyester, such as dimethylsulfoxide, dimethylformamide, dimethylacetamide and N-methylpyrrolidone, have different problems because they are relatively non-volatile, have high boiling points, and so are extremely difficult to remove, and also because of the unacceptable toxicity of some of these solvents. It has been possible to identify certain solvents for both components which are more volatile and which are toxicologically acceptable, but such solvents present other difficulties. **For example, acetic acid is a solvent for both peptides and polyesters, but the use of a large amount of acid solvent predisposes the peptide to exist as the acetate salt (because of mass action effects), so that the removal of the acetic acid at room temperature (say 20.degree.-25.degree. C.), or by freeze drying, results in phase separation of the peptide and the polyester, so that the desired salt formation tends not to occur.**
>
> [ ]
>
> The preparation of the peptide-polyester salts of this invention can be carried out using homo- or co-polyesters containing carboxylic acid groups, and peptides wherein the basic residues occur as the free base or as salts of a weak acid, preferably a volatile acid, having an acid dissociation constant of less than 10.sup.-3 or a pK.sub.a (pK.sub.a =-log.sub.10 K.sub.a, where K.sub.a is the acid dissociation constant) of greater than 3. **A particularly preferred such basic peptide salt is a salt with acetic acid. However, because of the inherent incompatibility of the two macromolecular species, particular conditions have to be used in which these peptide-polyester salts can be generated.**

[ ]

An example of the first approach is to use solvents such as, but not limited to, dimethylsulfoxide, dimethylformamide, dimethylacetamide and N-methylpyrrolidone, which are essentially neutral and which can be solvents for both the peptide and the polyester. Under normal circumstances, as indicated above, these solvents are extremely difficult to remove, due to their high boiling points and relative non-volatility. When a peptide (for example as an acetate salt) and a polyester are dissolved in one of these solvents, the peptide tends to exist as the salt with the polyester, as the more strongly acidic lactic or glycolic acid group in the polyester displaces the weaker carboxylic acid. **The bulk of the solvent and liberated acetic acid (or other weak but volatile carboxylic acid)** may be removed in vacuo, and the residual solution containing peptide-polyester salt is added to distilled water, to precipitate the insoluble polymeric salt.

[ ]

Thus, according to a further feature of this invention, there is provided a process for the manufacture of a salt comprising a basic peptide and a carboxy-terminated polyester, which comprises dissolving the basic peptide, in free base form or in the form of a salt with a weak acid, for example acetic acid, and the carboxy-terminated polyester in a neutral, polar solvent in which both are soluble, removing the solvent or most of the solvent, and adding the remaining concentrated solution to an excess of a non-solvent for the peptide-polyester salt.

The amount of direction provided by the inventor and the existence of working examples.

The description clearly provides for unexpected results using certain acids to stabilize peptides at 1.5 molar amount or more to the latter v. findings that less than 1.5 molar amount did not exert the same benefit of stabilization.

See description pages 65-73, test results of W/O emulsion w/ Glacial Acetic Acid as the acid, leuprolide acetate as the peptide active agent, and D,L Lactic Acid as the polymer:

"Addition of acetic acid makes it possible to obtain a W/O type emulsion satisfactorily and addition of mannitol into an outer aqueous phase makes it possible to improve the dispersibility of the obtained microspheres.

Experimental Example 1

[ ]

As seen in the Table i, a stable W/O type emulsion was obtained. The W/O type emulsion had a slightly high viscosity after emulsification for 8 minutes. Although the viscosity of the W/O type emulsion after emulsification for 5 minutes was also increased, it was not such a level as to cause a problem in production.

Comparative Example 1

[ ]

The viscosity of the W/O type emulsion was increased after emulsification for 4 minutes. As compared with Experimental Example 1 in which acetic acid was added, the viscosity of the W/O type emulsion was remarkably increased.

Experimental Example 2

Leuprorelin acetate (drug content: 97.4 %, acetic acid content: 6.0 %) (each 0.2061 g) was dissolved in aqueous acetic acid solutions having various concentrations (each 0.2116 g), and thereto was added a solution of a DL-lactic acid polymer (weight average molecular weight: 21,900) (1.82 g) in dichloromethane (3.15 g). The resulting mixtures were stirred with a vortex mixer for about 30 seconds to obtain W/O type emulsions. The appearances of the W/O type emulsions thus obtained were compared. The results are shown in Fig. i. In the W/O type emulsion prepared using acetic acid in a molar amount of about 1.8 times that of the drug, it seemed that small emulsion particles were formed. In the W/O type emulsion prepared using acetic acid in a molar amount of about 1.4 times that of the drug, the drug was gelatinized. In the W/O type emulsion prepared using acetic acid in a molar amount of about 1.6 times that of the drug, the drug was slightly gelatinized. Using acetic acid in a molar amount of about 1.8, 2.3 or 2.8 times that of the drug, a homogeneous emulsion was obtained. The W/O type emulsion prepared using acetic acid in a molar amount of about 1.8 times that of the drug had a bluish transparent color. On the other hand, the W/O type emulsion prepared using acetic acid in a molar amount of about 2.3 times or more that of the drug had a whitish emulsion color. The W/O

type emulsion prepared using acetic acid in a molar amount of about 1.7 times that of the drug had also a bluish transparent color.

From these results, it was found that the smallest emulsion particles were formed in the bluish transparent W/O type emulsion prepared using acetic acid in a molar amount of 1.7 to 1.8 times that of the drug.

Experimental Example 3

[ ]

The appearances of the W/O type emulsions thus obtained were compared. As a result, in the W/O type emulsion prepared using acetic acid in a molar amount of about 1.8 times that of the drug, it seemed that homogeneous emulsion particles were formed. In the W/O type emulsions prepared using acetic acid in a molar amount of about 1.3 and 1.4 times that of the drug, the oil phase and the inner aqueous phase were separated.

Experimental Example 4

[ ]

The appearances of the W/O type emulsions thus obtained were compared. As a result, in the W/O type emulsion prepared using acetic acid in a molar amount of about 1.8 times that of the drug, it seemed that homogeneous emulsion particles were formed. In the W/O type emulsions prepared using acetic acid in a molar amount of about 1.3 and 1.4 times that of the drug, the oil phase and the inner aqueous phase were separated.

Experimental Example 5

[ ]

As seen in Table 3, the microspheres of Example 1 produced by formulating only Peptide A could contain the physiologically active substance at a high trapping rate, and had excellent dispersibility. Further, the microspheres of Example 1 suppressed initial excessive release of the physiologically active substance and released the physiologically active substance at a constant rate over avery long period of time.

Experimental Example 6

An acetic acid salt of Peptide A (0.6 g) was dissolved in a 2 wt% aqueous acetic acid solution (0.65 g) (1.5 times or more the molar amount of Peptide A). To this solution, a solution of polylactic acid (weight average molecular weight; 21,000) (5.4 g in dichloromethane (9.45 g) was added. The resulting mixture was lightly dispersed by shaking it with a hand and then emulsified with Polytron (manufactured by Kinematica) for a predetermined time to obtain a W/O type emulsion. In the same manner except that the emulsification time was changed to various times, various emulsions were formed. The viscosities of the W/O emulsions thus obtained was measured. The results are shown in Fig. 2.

In the same manner as described above, Peptide A (0.6 g) was dissolved in a 2 wt% aqueous acetic acid solution (0.635 g) (less than 1.5 times the molar amount of Peptide A). To this solution, a solution of polylactic acid (weight average molecular weight; 21,000) (5.4 g) in dichloromethane (9.45 g) was added. The resulting mixture was lightly dispersed by shaking it with a hand and then emulsified with Polytron (manufactured by Kinematica) for a predetermined time to obtain a W/O type emulsion.

The W/O type emulsion prepared using acetic acid in a molar amount less than 1.5 times that of Peptide A had an increased viscosity when the emulsification time was relatively short. On the other hand, the W/O type emulsion prepared using acetic acid in a molar amount of 1.5 times or more that of Peptide A was stable and did not have an increased viscosity even if the emulsification time was short as shown in Fig 2, so that the W/O type emulsion could be prepared easily.

From these experimental results, it was found that the use of acetic acid in a molar amount of about 1.5 times or more that of a drug made it possible to obtain a stable W/O type emulsion and the use of acetic acid in a molar amount of about 1.65 times or more that of a drug made it possible to obtain an emulsion with relatively smaller particle size. Furthermore, it was confirmed that a lactic acid polymer or a lactic acid-glycolic acid polymer could be used as a polymer for an oil phase, which improved the productivity of final pharmaceuticals.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

Applicant has provided insufficient test data, or as it appears, even test data that correlates to the claimed invention, wherein the acid/base are to 1.5 molar amount or more than the active agent; without evidence of the polymer to be used, which could as claimed be a stronger acid and thus cancel the acid (or base) used in it's ability to "stabilize" the active agent (e.g. luprolide, in it's acetate form). However, a disclosure should contain representative examples, which provide

reasonable assurance to one skilled in the art that the compounds falling within the scope of a claim will possess the alleged utility. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The quantity of experimentation necessary needed to make or use the invention based on the disclosure:

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view to the quantity of experimentation necessary, the limited working examples noted above (test data on an acid/base:active agent molar amount not 1.5 molar amount of the former v. the latter; or evidence of what polymer is to be used therein, so as not to cancel out the acid/base's presumed "stabilizing" effect (e.g. acetate form0 on the active agent (e.g. peptide luprolide), the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. As noted supra, based on Hutchinson et al., the skilled artisan would not reasonably expect or have any certainty that the tested composition to stabilize the active agent, since it is not in a 1.5 or more molar amount thereof – presumed to somehow equate to the theory of stabilization for sustained release of the active agent. The limitations of exhibiting activities is not seen as providing requisite enablement, because even if the activities are specified as set forth above, the specific sequences necessary for these properties are still unknown. Thus, the teachings set forth in the specification provide no more than a plan or invitation for those skilled in the art to experiment practicing the claimed invention.

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 it is unclear what the metes and bounds of the claimed invention are as a "sustained-release composition" based on the claims read in light of the specification which wer only found to be W/O emulsions (water in oil). As a non- W/O emulsion is not certain as to it's effect hereon, based on distinguishable properties effect, Applicant may wish to consider amending the claims to positively modify the "sustained-release" aspect with the latter, providing support thereof, or address by evidence/argument.

In claim 1, the acid (or base) "in a molar amount of 1.5 or more times" to active agent is indefinite as claimed when read in light of the actual amounts of acid:active agent found throughout part/all of the specification? See para 236/240 to 15.5g leuprolide to .6g acetic acid, totaling 16.2 g. This example would appear to be showing the exact opposite in terms of molar amount ratio claimed? If necessary Applicant may wish to simply claim the range by g of acid to active agent to distinctly claim the invention. Or clarify by amendment or argument the discrepancy noted.

In claim 1, the metes and bounds of the physiologically active agent are uncertain. Only peptide as active agents, e.g. LHRH derivatives (claim 7), specifically leuprolide peptide (claim 8) are shown to be tested. Although the results shown can be deemed to extend to other peptides,

there is no evidence these results the 1.5 molar amount or more of acid/base would 'stabilize' a non-peptide active agent. Thus, it is uncertain what the metes and bounds of the invention of the invention as to active agent really are, per the invention as claimed?

In claim 1 it is unclear WHAT "an acid or base" is capable of being used "in a molar amount of 1.5 or more times" v. WHAT polymer, and the latters effect on the former if a stronger acid, as is entirely possible as claimed. HERE THE TEST RESULTS ALL SEEM TO BE RUN WITH THE ONLY AN ACID [NO BASE] OF GLACIAL ACETIC ACID AND ONLY A POLYMER OF D,L-LACTIC ACID. It is uncertain without undue experimentation if ANY acid (or base) or ANY polymer would carry out the same, but for those tested. [As opposed to the peptides used, even though only leuprolide acetate was used]. Applicant is asked to address with evidence how it could be certain without undue experimentation that ANY acid (or ANY base, not tested) and ANY polymer would work, especially without the latter cancelling out the former. OR amend the claims to be drawn to the specific acid and polymer tested. Thus the metes and bounds of the invention, as tested, have not been claimed.

Prior Art Made of Record But Not Relied Upon

WO 9937288 (Takeda Chemical), drawn to sustained release compositions (see entire document).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 9/28/2009

/Maury Audet/
Examiner, Art Unit 1654
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